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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,353	SCHUURMAN ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-11,13,15,17,19-24,28-30,32-34,36-38 and 40-108* is/are pending in the application.

4a) Of the above claim(s) *57-66,68-89,92-98,103 and 104* is/are withdrawn from consideration.

5)☒ Claim(s) *99-102* is/are allowed.

6)☒ Claim(s) *2-11,13,15,17,19-24,28-30,32-34,36-38,40-56,67 and 105-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 2-11, 13, 15, 17, 19-24, 28-30, 32-34, 36-38 and 40-108 are all the pending claims for this application.

2. Claims 57-66, 68-89, 92-98, 103 and 104 are withdrawn.

3. Claims 1, 12, 14, 16, 18, 90 and 91 were cancelled, Claims 2, 5-11, 13, 15, 17, 19, 40, 43, 46, 49 and 53-55 were amended to depend from Claims 51 and/or 52, and new Claims 105-108 were added in the Response of 2/8/07. Claims 105-108 are entered and raise issues of new matter as discussed infra.

4. Claims 2-11, 13, 15, 17, 19-24, 28-30, 32-34, 36-38, 40-56, 67, 99-102 and 105-108 are all the claims under examination.

5. Applicants amendments to the specification and claims have raised new grounds for objection and rejection.

Withdrawal of Objections

Specification

6. The objection to the specification for containing an embedded hyperlink and/or other form of browser-executable code (p.9, line 7; p. 57, lines 11-12) is withdrawn in view of the amendments to the specification shown on pp. 2-3 of the Response of 2/8/07.

7. The objection to the specification for the improper use of the trademark Zenapax® is withdrawn in view of the amendments to the specification shown on pp. 2 and 4-6 of the Response of 2/8/07.

Withdrawal of Rejections

Claims - 35 USC § 112, first paragraph

Written Description

8. The rejection of Claims 12, 14, 16 and 18 under 35 USC § 112, first paragraph, for lacking written support in the originally filed specification is withdrawn and rendered moot in view of the canceled claims. Applicant's comments on p. 26, ¶1 of the Response of 2/8/07 are acknowledged.

Enablement

9. The rejection of Claims 12, 14, 16, 18, 103 and 104 under 35 USC § 112, first paragraph, for lacking enablement is withdrawn and rendered moot in view of canceled claims 12, 14, 16 and 18, and in view of withdrawn Claims 103 and 104.

Claims - 35 USC § 103

10. The rejection of Claims 1-6 and 55 under 35 U.S.C. 103(a) as being unpatentable over Green (J. Immunol. Methods 231:11-23 (1999)) in view of Osterberg et al. (Biochemical Society Transactions 23:1038-1043 (1995)) and/or Henry et al. (Expert Opin. Pharmacother. 3(11):1657-1663 (2002)) is withdrawn in view of canceled Claim 1 and rendered moot with respect to Claims 2-5 and 55. Applicant's comments on p. 32 of the Response of 2/8/07 are acknowledged.

Rejections Maintained

Claims - 35 USC § 112, first paragraph

Written Description

11. The rejection of Claims 19 and 56 under 35 U.S.C. 112, first paragraph, for lack of written description support is maintained for reasons of record as set forth in the Office Action of 9/7/06.

Claim 19, element (ii) and dependent 56 are drawn to a human monoclonal antibody comprising HC and LC variable domains with binding specificity for CD25 where the variable domains are at least 90% homologous to the variable domains for the HC and LC of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14 and 16. Applicants have yet to demonstrate a single species of isolated antibody meeting all of these criteria in the originally filed application.

Applicant's allegation that the rejection is rendered moot because Claims 19 and 56 now depend from Claims 51 and 52 is not considered persuasive because they have not explained why the rejection is inapplicable (p. 26, ¶1 of the Response of 2/8/07). Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims is supported by the originally filed specification or in depending from Claims 51 or 52.

Further, the Examiner requests that Applicants draw attention to the subject matter of the canceled claims (Claims 12, 14, 16 and 18) and which is essentially recited in Claim 19 element (ii) for each of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14 and 16.

For all of these reasons the rejection is maintained.

Enablement

12. The rejection of Claims 7-11, 13, 15, 17, 19-24, 28-30, 32-34, 36-38, 40-50, 53, 54, 56, and 67 (Claims 2-6, 51, 52, 55 and 105-108 are added) under 35 U.S.C. 112, first paragraph, for lacking enablement is maintained for reasons of record as set forth in the Office Action of 9/7/06. Claims 2-6, 51, 52 and 55 rejected based on Applicants amendment of the claims to depend from Claims 51 and 52. New claims 105-108 are added for the reasons set forth below.

Applicant's allegations on pp. 26-32 of the Response of 2/8/07 and the 1.132 Declaration of Dr. van de Winkle in view of the art reference exhibits discussed below have been considered and are not found persuasive.

The interpretation of Claims 7-11, 13, 15, 17, 19-24, 28-30, 32-34, 36-38, 40-50, 53, 54, 56, and 67 is of record as set forth in the Office Action of 9/7/06. Claims 51 and 52 are drawn to any human CD25 antibody having a VH derived from a human V_H1-69/JH4b or V_H1-69/JH5b germline sequence and VL derived from human A27/J_k4 or A27/J_k5 germline sequence (claim 51) and any human CD25 antibody having a VH derived from a human V_H1-69/D7-27/JH4b or V_H1-69/D7-27/JH5b germline sequence and VL derived from human A27/J_k4 or A27/J_k5 germline sequence (claim 52). New Claims 105-108 are drawn to human Mabs binding to human CD25 having VH comprising CDR-13 and the VL comprising CDR1-3, where the VH CDR3 is SEQ ID

NO: 25 of AB7 (Claim 105), SEQ ID NO:31 of AB11 (Claim 106), SEQ ID NO:37 of AB12 (Claim 107) and SEQ ID NO: 19 of AB1 (Claim 108).

a) The specification is enabling for making fully human anti-CD25 (IL-2 receptor) monoclonal antibodies, AB7, AB12, AB1 or AB11, with the XenoMouse technology having a K_D of about 10^{-8} M or less, and using the antibodies to: inhibit binding of IL-2 to CD25; inhibit anti-CD3 induced T cell proliferation of PBMCs; inhibit MLR; and internalize CD25 expressed on T cells.

b) The specification is not enabling for making or expressing any human anti-human CD25 antibody from a XenoMouse animal.

The specification is not enabling for making or expressing from the germline sequences, human V_H1-69/JH4b or V_H1-69/JH5b and human A27/J_k4 or A27/J_k5; and human V_H1-69/D7-27/JH4b or V_H1-69/D7-27/JH5b and human A27/J_k4 or A27/J_k5, a diversity of human anti-human CD25 antibodies much less a monoclonal and which meets all of the criteria of the claimed invention including:

having the isotype of IgG2, IgG3, IgG4, IgM, IgA1, IgA2, secretory IgG, IgD and IgE;

having a dissociation equilibrium constant (K_D) of about 10^{-8} M or less, preferably of about 10^{-9} M or less, more preferably of about 10^{-10} M or less, or 10^{-11} M or even less from human CD25; and

having one or more of the following characteristics of (a) specificity for human CD25; (b) inhibits binding of IL-2 to CD25; (c) eliminates T cells expressing CD25; (d) tolerizes T cells; (e) inhibits proliferation of T cells expressing CD25; (f) inhibits anti-CD3

antibody-induced T cell proliferation of peripheral blood; (g) inhibits mixed lymphocyte reaction (MLR); and (h) internalization of CD25 expressed on T cells.

Applicants have identified and characterized *only* four (4) anti-human CD25 antibody clones (AB1, AB7, AB11 and AB12) expressed from the germline gene sequence from HCo mice ((CMD)++; (HCo7) 11952+; (JKD) ++; (KCo5) 9272+ genotype) and *all* were IgG1, kappa (p. 56, lines 7-11). The specification does not appear to teach the total number of hybridoma clones from each genotype that were actually required to be screened in order to identify clones having the binding specificity, affinity and functional properties as instantly claimed (Claims 2 and 4-6). On p. 54 at lines 14-19 of the specification, the total number of spleenocytes used for the fusion step were 4 $x10^8$ (HCo7 genotype), 2.6 x 10^8 (HCo12 genotype), 2.4 $x10^8$ (HCo7 genotype), 2 x 10^8 (HCo7 genotype) and 1.9 x 10^8 (HCo7 genotype). Assuming *arguendo* all of the fused spleenocytes remained viable after the fusion step, then only four hybridoma clones meeting all of the claimed criteria were isolated from a total of 12.9 x 10^8 hybridoma clones and from only the HCo 7 mouse genotype.

The specification does not appear to teach the specific gene usage of the 4 clones but it is expected that it would be highly conserved amongst the 4 clones. Davis et al. (1999) Can. Metastasis Rev. 18:421-425 describes neutralizing antibodies for epidermal growth factor receptor produced from XenoMouse animals shared similar gene composition and out 8 clones each shared one of 2 VH genes (Table 3). Davis teaches "there appear to be rigorous structural requirements for antibodies that bind effectively to the ligand binding site on EGFr" (p. 425, Col. 1). Gallo et al. Eur. J.

Immunol. (2000) 30:534-540 compared XenoMouse and human VH gene segment usage for the VH3 and VH4 gene segments and found the same genes to utilized and to the same degree, thus the VH gene segmentation representation in the XenoMouse repertoire appears to be substantially the same as observed in humans (Figures 1 and 2). Similar findings were reported for JH gene segments between human and XenoMouse repertoires (Table 3).

Thus one skilled in the art could not have practiced or would have expected to obtain any class of human anti-CD25 antibody having structural diversity from a transgenic mouse and meeting all the functional properties for a human CD25 antibody as broadly encompassed by the claims.

c) The specification and the prior art are not enabling for using a CDR3 domain alone to generate antibodies having the same antigen specificity.

From sequence alignments of the heavy chain variable region sequences (see Figure 2), the 4 antibodies were derived from the HCo7 germline gene. Upon analysis of these 4 sequences none have the same sequences. Analysis of the VH CDR regions show all 4 have different CDR3 sequences. In addition, the antibodies also have some differences in the CDR1 and CDR2 sequences. Additionally, there are essentially no changes (changes at 2 positions) in the framework regions. From sequence alignments of the VL sequences the 4 antibodies have different CDR3 sequences and different residues in CDR1 and identical CDR2 sequences. In addition, there are essentially no changes (only changes in 3 positions) in the framework regions.

The specification describes that the antibody variable heavy chains were only paired with specific variable light chains, however the specification suggests that one could mix and match the variable light and variable heavy chain regions between antibodies but no data is shown.

Applicant's allegations set forth on pp. 26-29 of the Response of 2/8/07 are that it was well established in the art at the time the application filing date (with priority to 11/15/02) that the CDR3 domain alone can determine the specificity of an antibody and, importantly, that multiple antibodies can be predictably generated based on a common CDR3 sequence, without undue experimentation. For example, the following references provide evidence supporting these art recognized aspects of antibody architecture and binding, and the role of the CDR3 region in particular: Klimka *et al.* (2000) British J. of Cancer 83(2):252-260; Beiboer *et al.* (2000) J. Mol. Biol. 296:833-849; Rader *et al.* (1998) PNAS USA 95:8910-8915; Barbas *et al.* (1994) 116 J. Am. Chem. Soc. 2161-2162; Barbas *et al.* (1995) 92 PNAS USA 2529-2533; and Ditzel *et al.* (1996) 157 J. of Immunol. 739-749.

The arguments state that Klimka *et al.* describe the production of a humanized anti-CD30 antibody using only the heavy chain variable CDR3 domain, *i.e.*, the major determinant for epitope-specificity, of a murine anti-CD30 antibody, Ki-4. The argument also states Beiboer *et al.* generated recombinant antibodies using only the heavy chain CDR3 sequence of a parent antibody. Specifically, the authors engineering an antibody to epithelial glycoprotein-2 (EGP-2) by retaining only the murine heavy chain CDR3 domain of the murine MOC-31 antibody.Similarly, the argument states using only the

CDR3 sequence of a parent antibody, Rader *et al.* describe the production of a humanized anti-integrin $\alpha_v\beta_3$ antibody using the heavy and light chain variable CDR3 domains of the murine anti-integrin $\alpha_v\beta_3$ antibody, LM609.

With regard to these arguments, while the art recognizes the importance of CDR3 in antigen binding, the Klimka et al, Beiboer et al, and Rader et al references do not provide support for stating that CDR3 alone is only needed for specificity.

Klimka et al describe a screening method for selection of antibodies binding to CD30 by fist screening libraries of human variable heavy chains of CDR1 and 2 and framework regions (FR) 1, 2, and 3 (see Figure 1). The rest of the variable heavy chain was CDR3 and framework 4 of the mouse paired with the entire mouse light chain variable region. This resulted in obtaining an antibody that bound CD30 and had human CDR1, 2, and FR 1, 2 and 3. Klimka et al next took this molecule and screened a human variable light chain library for CD30 binders. This resulted in obtaining an antibody that had a human variable light chain region. Thus, the final molecule is an antibody comprising only the mouse CDR3 variable region and FR4 of the mouse antibody.

Beiboer et al describe a screening method where the entire variable region of the mouse antibody is used to screen a human variable library and a light chain determined that paired with the heavy chain. Then the light chain was screened against a heavy chain library with CDR3 retained from the mouse sequence.

Rader et al describe using the mouse heavy chain variable region and screening this against a human light chain library with CDr3 of the mouse light chain retained.

Then a light chain is determined and screened against a human library of heavy chains with the CDR3 of the mouse retained (see Figure 1).

A central theme in the art (citations below as well as art cited by applicants) is that while the sequence of CDR3 may be indicated as being important in binding, it is the conformation of the CDR3 as well as the contribution of other CDRs and frameworks are essential for retaining the conformation of the antigen binding site in an antibody. This is underscored in the references of Klimka et al, Beiboer et al, and Rader et al cited above. In discussing Klimka et al, this reference first screened using the mouse light chain variable region. Klimka et al did not just screen human libraries with only the mouse CDR3 region retained. Klimka et al first found human heavy chain variable regions from a human library that would be compatible with the mouse CDR3 of the heavy chain and the entire mouse variable light chain. Klimka et al found antibodies that retained the conformation of the CDRs as well as found FRs that would support the conformation of the CDR3. Thus, Klimka et al demonstrates that while CDR3 of the heavy chain is important for antigen binding the contributions of other regions, i.e. other CDRs and FRs are also important for structural integrity for antigen binding.

A similar situation exists in the Beiboer et al and Rader references. The antibody variable chains were first screened by keeping the mouse variable region constant and screening for human variable regions and then using the selected variable region to screen for the other variable chain.

Thus, the screening methods described in Klimka et al, Beiboer et al, and Rader et al never only kept the CDR3 region of the molecule constant and totally randomized

the other residues in the variable region that contained the constant CDR3 and screened against a totally random complementary library. In other words the references do not describe a method where only CDR3 in the mouse was constant and the rest of the molecule is random. The methods described used methods to retain the conformation of the parent antibody binding site.

The argument further states that further evidence showing that functionally equivalent recombinant antibodies could indeed be generated without undue experimentation at the time of the relevant filing dates using only the CDR3 sequence of a parent antibody and, importantly, the predictability of generating multiple antibodies having the same binding specificity based on a common CDR3 sequence is provided by Barbas *et al.* (1994) who describe a method for generating antibodies having high affinity for double-stranded DNA. In particular, Barbas *et al.* successfully generated isolated antibodies by antigen selection from synthetic libraries which utilized the same heavy chain with randomized CDR3 sequences. The authors concluded that the CDR3 provides the most significant contribution to antigen binding (page 2161, left column, second full paragraph).

With regard to this argument, while CDR3 may be important this reference again seems to indicate that while one could find antigen binders by randomizing CDR3 the rest of the molecule was constant and again suggests that the conformation of the binding site is extremely important. The residues held constant influence the binding conformation of the CDR3.

The argument continues stating moreover, in a separate publication, Barbas *et al.* (1995) also describe grafting the heavy chain CDR3 sequences of three Fabs, SI-1, SI-40 and SI-32, against human placental DNA onto the heavy chain of an anti-tetanus toxoid Fab, thereby, replacing the existing heavy chain CDR3. The results of these studies showed that grafted Fabs produced binding to DNA (page 2532, second paragraph, and the Abstract) and, thus, that the CDR3 alone conferred binding specificity.

Similarly, Ditzel *et al.* also describe grafting studies which showed that a heavy chain CDR3 only can be transferred to the heavy chain of another antibody and retain the same binding specificity.

With regard to this argument, while the references do show only CDR3 was grafted into another antibody, the frameworks from the donor and acceptor were highly homologous. In addition, Ditzel et al state that although CDR3 of the heavy chain is important, the frameworks may still have some influence on polyreactivity (see page 748, left col) and in fact the peptide that Ditzel et al made to mimic the CDR3 region contained some framework residues and also was in a constrained conformation by a disulfide bond at the base of the peptide

Although Barbas et al and Ditzel et al transferred only CDR3 of the heavy chain these two references do not overcome the unpredictability in the art as far as demonstrating that CDR3 is only needed for binding.

In fact there are numerous publications which acknowledge as indicated above that while CDR3 is important, the conformation of other CDRs as well as FR influence binding.

MacCallum et al. J. Mol. Biol. (1996) 262, 732-745, analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). Additionally Pascalis et al. The Journal of Immunology (2002) 169, 3076-3084 demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al. (2003) BBRC 307, 198-205, which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue

located just before the H3 (see page 202, left col.). Vajdos et al. (2002) J. Mol. Biol. 320, 415-428, additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.). Holm et al (2007) Mol. Immunol. 44: 1075-1084 describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen et al. J. Mol. Bio. (1999) 293, 865-881 describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu et al. J. Mol. Biol. (1999) 294, 151-162 state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that CDR3 makes a significant contribution in the heavy chain and perhaps the light chain in antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support "that it was clearly established in the art, at the time the applications were filed, that the heavy chain CDR3 alone is sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a

common CDR3 sequence. The foregoing publications also evidence that, once provided with the CDR3 sequence of a given antibody, it was well within the ordinary skill of the art to have generated other antibodies having the same CDR3 region and binding specificity, yet having different CDR1, CDR2 and framework regions." Analyzing applicants own disclosure which while it does have divergent CDRH3 residues, the majority of these heavy chains were paired with specific light chains. Additionally, the data seem to indicate that it is the frameworks and other CDRs that contribute to antigen binding because the data show that the majority of the antibodies disclosed have highly homologous sequences outside the CDR3 regions. Further, there are no examples of mixing or matching of the light chains or heavy chains and most importantly there is no examples of placing only CDR3 of the heavy and/or CDR3 or the light chain in just any framework and producing an antibody that binds antigen as broadly claimed or suggested.

d) The specification and the prior art are not enabling for making any conservative amino acid substitutions within CDRs that do not remove antibody binding.

Applicant's allegations set forth on pp. 29-32 of the Response of 2/8/07 are that it was well established in the art at the time the application filing date (with priority to 11/15/02) that the CDR domains are amenable to conservative modifications that do not abolish antigen binding and would not require undue experimentation. For example, the following references provide evidence supporting these art recognized aspects of conservative amino acid substituted CDRs in particular: Brummell et al. (1993)

Biochem. 32:1180-1187; Kobayashi et al. (1999) Protein Eng. 12(10):879-884; and Burks et al. (1997) PNAS USA 94:412-417.

The arguments state that Brummell *et al.* describe heavy chain CDR3 mutants for Salamonella with a wide number of substitutions except Gly^{102H} allowing antigen binding. The argument also states Kobayashi *et al.* generated Tyr or Phe substituted Trp (H33) residue with moderate loss of affinity and replacement with Arg having greater loss. Burks *et al.* describe the production of mutated anti-digoxin analog antibodies having conservative and non-conservative substitutions.

With regard to these arguments, while the art recognizes conservative substitutions in CDRs in antigen binding, the Brummell *et al.*, Kobayashi *et al.* and Burks *et al.* references do not provide support for stating that any conservative amino acid substitution within in a CDR would retain antigen binding or would not alter other characteristics of the antibody.

Brummell *et al.* found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody (Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobatashi *et al.* discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr substitutions at Trp 33 retained "a large fraction of the

wild-type binding affinity, while the Ala substitution diminished antigen binding" (Table 1). However, Kobayashi notes "replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv" (p. 883, Col. 2, ¶3).

Burks *et al.* discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxignenin and oubain. Histogram analysis of the mutants (Figure 2) reveals that "not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Although Brummell *et al.*, Kobatashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects these three references do not overcome the unpredictability in the art as far as demonstrating that any conservative substitution within any CDR can be made without affecting binding.

Numerous publications acknowledge that conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity. Jang et al. (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFV derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4). And Brorson et al. (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs

of IgM Abs for the bacterial protein, levan, are ablated. Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, "a very conservative substitution may abolish binding" while "in another, a non-conservative substitution may have very little effect on the binding" (p. 35, Col. 1, ¶1).

Thus, it is unlikely that just any human CD25 antibody having a conservative amino acid substitution, as defined by the claims would have the required binding function (Claim 5) in addition to any one or more other property (Claim 6). The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Furthermore, while the level of skill required to generate a recombinant CDR-substituted antibody is that of a molecular biologist or molecular immunologist, the skilled artisan would have been required to characterize the parent antibody, identify candidate amino acid residues for substitution in the FR and CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure human CD-25 binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K.sub.D), dissociation and association rates (K.sub.off and K.sub.on respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or

more of the characteristics recited in elements b-h of Claim 6. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified, anti-CD-25 antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid substitutions encompassed by the claims would result in *just any* substituted antibody clone having retained the antigen binding activity (Claim 5) in addition to having one or more other properties (Claim 6) (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

New Grounds for Objection

Sequence Listing/New Matter

13. Applicant's request to enter a revised Sequence Listing of 2/8/07 in order to correct a "typographical error in SEQ ID NO:38" has not been considered or entered but is placed in the file. Applicants have not identified the error in the sequence from the original Sequence Listing of 6/29/06 nor have they identified where original support for the "corrected" sequence of SEQ ID NO:38 can be found in the application as filed. Absent evidence to the contrary, the revised sequence for SEQ ID NO:38 raises an issue of new matter.

Specification/New Matter

14. Applicant's request on p. 25, ¶1 of the Response of 2/8/07 to amend the specification to replace the Sequence Listing of 6/29/06 with the revised Sequence Listing is considered but not entered for the reasons set forth supra.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 2-11, 13, 15, 17, 19-21, 40-56 and 67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 2-11, 13, 15, 17, 19-21, 40-56 and 67 are indefinite for the recitation "derived from...germline sequence" in Claims 51 and 52, because the exact meaning of the term "derived" is not clear. The term "derived" is not one, which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the ascertainable meaning for this phrase. Since it is unclear how the VH or VL domains are to be derivatized to yield the class of isolated antibodies referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of antibodies to the phrase. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass V domains with amino acid substitutions, insertions, deletions. Thus it is not apparent what diversity for any of the antibodies is contemplated by the term "derived". In the absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

b) Claims 2-11, 13, 15, 17, 19-21, 40-56 and 67 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the transgenic mouse comprising the genetically inserted germline sequences of Claims 51 and 52. The application describes the production of human antibodies by immunizing a transgenic mouse (XenoMouse) with human CD25 antigen and producing human antibodies in the transgenic mouse. From screening

analysis four human antibodies directed to CD25 were obtained. Thus the claims encompass obtaining an infinite number of human CD25 antibodies from the human germline sequences even from within a human.

c) In the present instance, claim 5 recites the broad recitation for a dissociation equilibrium constant (K_D) of "about 10^{-8} M or less", and the claim also recites "preferably of about 10^{-9} M or less" followed by "more preferably of about 10^{-10} M or less, or 10^{-11} M or even less", which is the narrower statement of the range/limitation. (A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949)).

Conclusion

16. Claims 99-102 are drawn to a human anti-CD25 antibody that inhibits IL-2 binding to CD25 and has: VH CDR1-3 comprising SEQ ID NOS:35-37 and VL CDR1-3 comprising SEQ ID NOS:38-40 (AB12); VH CDR1-3 comprising SEQ ID NOS:17-19 and VL CDR1-3 comprising SEQ ID NOS:20-22 (AB1); VH CDR1-3 comprising SEQ ID NOS:23-25 and VL CDR1-3 comprising SEQ ID NOS:26-29 (AB7); and VH CDR1-3 comprising SEQ ID NOS:29-31 and VL CDR1-3 comprising SEQ ID NOS:32-34 (Ab11), respectively, and appear to be free of prior art.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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